

Statistical analysis of association between
urinary perchlorate and serum levels of
TSH and T4 in the NHANES cohort:
Consideration of gender, iodine status,
smoking, and thiocyanate

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Office of Environmental Health Hazard Assessment

- Mission: to protect and enhance public health and the environment by scientific evaluation of risks posed by hazardous substances.
- OEHHA develops guidance values for air, water, soil, and exposure to carcinogens and reproductive toxicants (Prop 65)

Public Health Goal Program

- Public Health Goals (PHGs) are developed for all regulated water contaminants
- PHGs are based entirely on public health protection, without consideration of cost or feasibility
- PHGs must be protective of the health of individuals drinking the water for a lifetime and must take into account sensitive populations including pregnant women and their fetuses, infants, and the elderly

Perchlorate

Blocks
the NIS

Inhibits
iodine
uptake

Decreases thyroid
hormone
production

Increases
TSH

Cognitive and other
effects, especially in
susceptible people
(iodine deficient,
pregnancy, fetus)

?

Do environmental perchlorate exposures cause adverse thyroid effects?

Perchlorate PHG

- Completed in 2004, based on the study of Greer et al. in human volunteers
- PHG intended to avoid any detectable inhibition of iodine uptake, with adequate margin of safety
- PHG level = 6 ppb

NHANES Data Evaluation

Objectives:

- Assess the impact of various factors on the relationship between urinary perchlorate and serum thyroxine (T4) and thyroid stimulating hormone (TSH)
- Evaluate females with urinary iodide <100 $\mu\text{g}/\text{L}$ (35% of the females in this sample) to compare our results with those of Blount et al. (2006)

Methods

- Univariate and multiple regression models of the NHANES data were developed in SAS 9.1
- Major parameters analyzed:
 - Urinary perchlorate, iodide, creatinine, nitrate, thiocyanate
 - Serum T4 and TSH
 - Smoking status

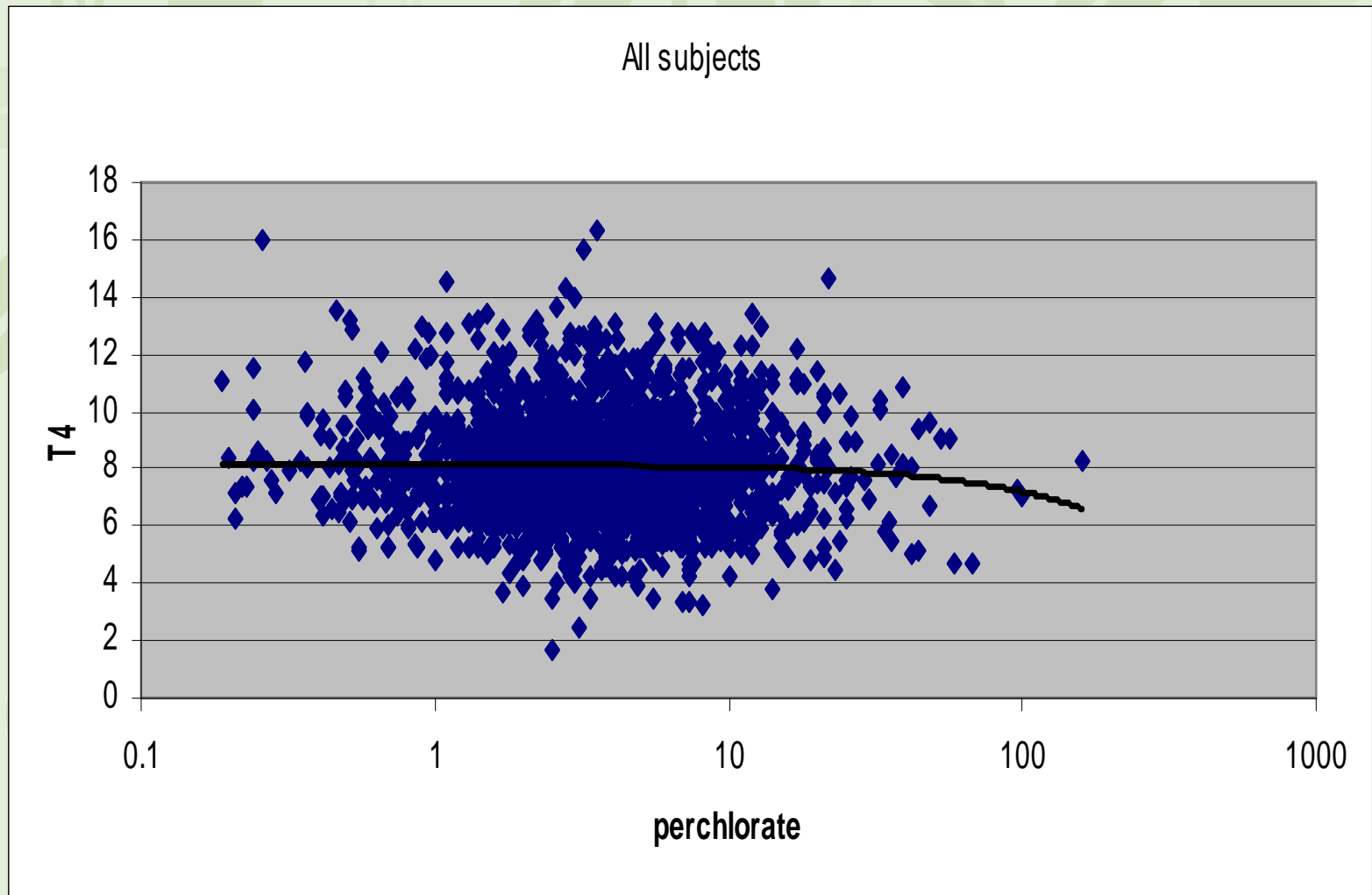
Methods, continued

- Other parameters evaluated:
 - sex, age, race, serum albumin, body mass index, 24-hr caloric intake
 - pregnancy, menopause, menarche, lactation status
 - serum c-reactive protein, hours of fasting before serum collection, use of thyroid-related medications

Methods, continued

- Urinary perchlorate and creatinine, and serum TSH were log₁₀ transformed to normalize their distributions
- Urinary creatinine added to all regression models involving urinary perchlorate, nitrate, and thiocyanate to adjust for variations in urinary output
- In univariate analyses, urinary perchlorate residuals adjusted for creatinine calculated by method described by Willet and Stampfer (1998)

Perchlorate (NHANES 2001-2002)



Results

- Univariate and multivariate analyses on all men and all women showed no clear effects or interactions with serum thyroid hormones
- Women with urinary iodide $<100 \mu\text{g/L}$ showed substantial evidence of interactions of interest
- Interactions of urinary perchlorate, cotinine, and thiocyanate, and smoking, with serum T4 or log TSH levels were most prominent

Parameters of interest in women with urinary iodine < 100 $\mu\text{g/L}$

	Current smokers	Non-smokers
N	66	260
Perchlorate ($\mu\text{g/L}$)	2.5 (0.55)	3.2 (0.88)
Iodine ($\mu\text{g/L}$)	51.7 (3.7)	54.3 (2.2)
Thiocyanate ($\mu\text{g/L}$)	4344 (646)	813 (64)
Cotinine (ng/ml)	201 (15.7)	1.1 (0.60)
T4 ($\mu\text{g/dL}$)	8.6 (0.22)	8.2 (0.18)
logTSH ($\mu\text{g/dL}$)	0.12 (0.06)	0.14 (0.03)

Associations between log perchlorate and serum T4 and log TSH in women with urinary iodine < 100 µg/L

	T4 ^a				logTSH ^b			
	N	b	SE	p	N	b	SE	p
All	362	-0.73	0.22	0.004	369	0.13	0.05	0.02
Smoking ^c								
Current	63	-1.66	0.37	0.0005	62	0.13	0.11	0.23
Non-smoker	245	-0.54	0.23	0.04	245	0.11	0.03	0.009
Cotinine in serum								
High (>10 ng/ml)	64	-1.47	0.30	0.0002	68	0.15	0.08	0.09
Medium ^d	185	-0.57	0.25	0.03	192	0.10	0.06	0.09
Low (ND)	101	-0.16	0.29	0.59	106	0.11	0.05	0.04
Thiocyanate in urine (tertiles)								
High (>1800 µg/L)	78	-1.67	0.40	0.0009	82	0.13	0.09	0.19
Medium	107	-0.68	0.37	0.09	108	0.20	0.04	0.0003
Low (<751 µg/L)	176	-0.49	0.30	0.11	178	0.10	0.05	0.06

Results summary

- Perchlorate negatively associated with T4 and positively associated with logTSH in women with urinary iodine < 100 $\mu\text{g}/\text{L}$
- The T4 negative association much greater in smokers
- The logTSH positive association not much affected by smoking

Univariate Analyses

Smoking, urinary cotinine, and urinary thiocyanate were not associated with serum T4 or TSH in women with urinary iodine $<100 \mu\text{g/L}$

Example:

- Cotinine with T4, $b = 0.03$, $p = 0.73$; with log TSH, $b = -0.02$, $p = 0.26$ ($n = 382$)
- Cotinine, adjusted for creatinine T4, $b = -0.17$, $p = 0.46$; for logTSH, $b = -0.05$, $p = 0.21$ ($n = 384$)

Combined Factor Analysis

Compare mean T4 and log TSH in women:

- Group 1: Current smokers, perchlorate residual >median, and urinary iodine <100 $\mu\text{g/L}$
- Group 2: Never smokers, perchlorate residual \leq median, and urinary iodine \geq 100 $\mu\text{g/L}$

Combined Factor Analysis

	T4		Log TSH	
	Mean	95% CI	Mean	95% CI
Group 1 (n=21)	7.16	6.28-8.05	0.24	0.13-0.36
Group 2 (n=161)	8.41	7.96-8.86	0.11	0.08-0.14
Difference	1.25		0.13	
p-value	0.04		0.001	

Summary

- Observations of Blount et al. (2006) for low-iodide women have been confirmed
- The relationship of perchlorate with T4 is $>$ in smokers than in nonsmokers, and in women with higher thiocyanate excretion
- The strength of the associations makes them unlikely to be due to chance
- The results seem biologically plausible

Using the Data

- How should this effect be used in risk assessment?
- How should other effects and associations discovered with this technology be used in risk assessment?

Using the Data

- Waiting for confirmation
- Need to decide on threshold effect of concern
- Need principles applicable to other alterations of homeostasis
- Need to allow for combined effects
- Need to address the sensitive subpopulation issues

Risk Communication

- This is a perchlorate exposure issue, not just a food or drinking water issue
- Should recommendations for use of iodine supplements be strengthened?
- Should iodination of salt be mandated?
- Should these results be mentioned in anti-smoking campaigns?

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